



## General

### Guideline Title

Treatment and prevention of heparin-induced thrombocytopenia: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines.

### Bibliographic Source(s)

Linkins LA, Dans AL, Moores LK, Bona R, Davidson BL, Schulman S, Crowther M. Treatment and prevention of heparin-induced thrombocytopenia: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012 Feb;141(2 Suppl):e495S-530S. [182 references] [PubMed](#)

### Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Warkentin TE, Greinacher A, Koster A, Lincoff AM. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008 Jun;133(6 Suppl):340S-80S. [284 references]

## Recommendations

### Major Recommendations

The grades of recommendation (1A, 1B, 1C, 2A, 2B, 2C) and the approach to rating the quality of evidence are defined at the end of the "Major Recommendations" field.

#### Screening for Heparin-Induced Thrombocytopenia (HIT)

Platelet Count Monitoring Combined with the 4Ts Score for Patients Receiving Heparin/Low- Molecular-Weight heparin (LMWH)

For patients receiving heparin in whom clinicians consider the risk of heparin-induced thrombocytopenia (HIT) to be >1%, the expert panel suggests that platelet count monitoring be performed every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first) (Grade 2C). (See Table 2, "[Overview of HIT] Incidence of HIT According to Patient Population and Type of Heparin Exposure," in the original guideline document.)

For patients receiving heparin in whom clinicians consider the risk of HIT to be <1% (see Table 2 in the original guideline document), the expert panel suggests that platelet counts not be monitored (Grade 2C).

#### Management of HIT Complicated by Thrombosis

## Discontinue Heparin or Initiate Vitamin K Antagonists (VKAs) vs Treatment with Nonheparin Anticoagulants

In patients with HIT complicated by thrombosis (HITT), the expert panel recommends the use of nonheparin anticoagulants, in particular lepirudin, argatroban, and danaparoid, over the further use of heparin or LMWH or initiation/continuation of a VKA (Grade 1C).

### Choice of Nonheparin Anticoagulants in Patients with HITT

#### *Normal Renal Function*

In patients with HITT who have normal renal function, the expert panel suggests the use of argatroban or lepirudin or danaparoid over other nonheparin anticoagulants (Grade 2C).

*Remarks:* Other factors not covered by the panel's analysis, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

#### *Renal Insufficiency*

In patients with HITT and renal insufficiency, the expert panel suggests the use of argatroban over other nonheparin anticoagulants (Grade 2C).

### Platelet Transfusions

In patients with HIT and severe thrombocytopenia, the expert panel suggests giving platelet transfusions only if bleeding or during the performance of an invasive procedure with a high risk of bleeding (Grade 2C).

### Starting a VKA before Platelet Recovery

In patients with strongly suspected or confirmed HIT, the expert panel recommends against starting VKA until platelets have substantially recovered (i.e., usually to at least  $150 \times 10^9/L$ ) over starting VKA at a lower platelet count and that the VKA be initially given in low doses (maximum, 5 mg of warfarin or 6 mg phenprocoumon) over using higher doses (Grade 1C).

The expert panel further suggests that if a VKA has already been started when a patient is diagnosed with HIT, vitamin K should be administered (Grade 2C).

*Remarks:* The expert panel places a high value on the prevention of venous limb gangrene and a low value on the cost of the additional days of the parental nonheparin anticoagulant.

### Discontinuing Thrombin Inhibitor after a Minimum of 5 Days of Overlap with a VKA

In patients with confirmed HIT, the expert panel recommends that the VKA be overlapped with a nonheparin anticoagulant for a minimum of 5 days and until the international normalized ratio (INR) is within the target range over shorter periods of overlap and that the INR be rechecked after the anticoagulant effect of the nonheparin anticoagulant has resolved (Grade 1C).

## Management of Isolated HIT (HIT without Thrombosis)

### Discontinue Heparin or Initiate VKA vs Treatment with Nonheparin Anticoagulants

In patients with isolated HIT (HIT without thrombosis), the expert panel recommends the use of lepirudin or argatroban or danaparoid over the further use of heparin or LMWH or initiation/continuation of a VKA (Grade 1C).

### Choice of Nonheparin Anticoagulants in Patients with Isolated HIT

In patients with isolated HIT (HIT without thrombosis) who have normal renal function, the expert panel suggests the use of argatroban or lepirudin or danaparoid over other nonheparin anticoagulants (Grade 2C).

*Remarks:* Other factors such as drug availability, cost, and ability to monitor the anticoagulant effect may influence the choice of agent. The dosing considerations are the same as for patients with HITT (see section 3.2 in the original guideline document). For a recommendation on choice of nonheparin anticoagulants in the setting of renal insufficiency, see the recommendations above under "Choice of Nonheparin Anticoagulants in Patients with HITT."

## Management of Patients with Acute HIT or Subacute HIT in Special Situations

### Patients Who Require Urgent Cardiac Surgery

In patients with acute HIT (thrombocytopenic, HIT antibody positive) or subacute HIT (platelets recovered but still HIT antibody positive) who require urgent cardiac surgery, the expert panel suggests the use of bivalirudin over other nonheparin anticoagulants and over heparin plus antiplatelet agents (Grade 2C).

In patients with acute HIT who require nonurgent cardiac surgery, the expert panel recommends delaying the surgery (if possible) until HIT has resolved and HIT antibodies are negative (see "Patients with a History of HIT Who Require Cardiac Surgery," below) (Grade 2C).

*Remarks:* Other factors not covered by our analysis, such as drug availability, cost, and ability to monitor the anticoagulant effect may influence the choice of agent. For recommendations for patients with a past history of HIT (>3 months previous) who require cardiac surgery, see the section "Patients with a History of HIT Who Require Cardiac Surgery."

#### Patients Who Require Urgent Percutaneous Coronary Interventions (PCI)

In patients with acute HIT or subacute HIT who require PCI, the expert panel suggests the use of bivalirudin (Grade 2B) or argatroban (Grade 2C) over other nonheparin anticoagulants.

*Remarks:* Other factors, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

#### Patients Who Require Renal Replacement Therapy

In patients with acute or subacute HIT who require renal replacement therapy, the expert panel suggests the use of argatroban or danaparoid over other nonheparin anticoagulants (Grade 2C).

*Remarks:* The expert panel acknowledges that the cost of argatroban may be prohibitive at some clinical centers. The expert panel further suggests that if the prothrombotic state of HIT appears to have resolved (as seen by normalization of the platelet count), saline flushes during dialysis would be a reasonable option. This suggestion is based on the presumed pathogenesis of thrombosis in this condition and not on the results of clinical trials.

#### *Patients with a Past History of HIT*

In patients with a past history of HIT who require ongoing renal replacement therapy or catheter locking, the expert panel suggests the use of regional citrate over the use of heparin or LMWH (Grade 2C).

#### Pregnant Patients

In pregnant patients with acute or subacute HIT, the expert panel suggests danaparoid over other nonheparin anticoagulants (Grade 2C). The expert panel suggests the use of lepirudin or fondaparinux only if danaparoid is not available (Grade 2C).

*Remarks:* Other factors, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

#### Management of Patients with a Past History of HIT

##### Patients with a History of HIT Who Require Cardiac Surgery

In patients with a history of HIT in whom heparin antibodies have been shown to be absent who require cardiac surgery, the expert panel suggests the use of heparin (short-term use only) over nonheparin anticoagulants (Grade 2C).

In patients with a history of HIT in whom heparin antibodies are still present who require cardiac surgery, the expert panel suggests the use of nonheparin anticoagulants (see the recommendation above under "Patients Who Require Urgent Cardiac Surgery") over heparin or LMWH (Grade 2C).

##### Patients Who Require PCI

In patients with a history of HIT who require cardiac catheterization or PCI, the recommended treatment is the same as above under "Patients Who Require Urgent Percutaneous Coronary Interventions."

##### Patients Who Require Prophylaxis or Treatment of Thrombosis

In patients with a past history of HIT who have acute thrombosis (not related to HIT) and normal renal function, the expert panel suggests the use of fondaparinux at full therapeutic doses until transition to a VKA can be achieved (Grade 2C).

#### Definitions:

## Grading of Recommendations Assessment, Development and Evaluation (GRADE) Approach to Rating Quality of Evidence

Study Design	Quality of Evidence	Lower if	Higher if
Randomized Trial →	High	Risk of bias -1 Serious -2 Very serious	Large effect +1 Large +2 Very large
	Moderate		
Observational Study →	Low	Inconsistency -1 Serious -2 Very serious  Indirectness -1 Serious -2 Very serious  Imprecision -1 Serious -2 Very serious  Publication bias -1 Likely -2 Very likely	Dose response +1 Evidence of a gradient  All plausible confounding +1 Would produce a demonstrated effect or  +1 Would suggest a spurious effect when result show no effect
	Very Low		

## Strength of the Recommendations Grading System

Grade of Recommendation*	Benefit vs. Risk and Burdens	Methodologic Quality of Supporting Evidence	Implications
Strong recommendation, high-quality evidence, Grade 1A	Benefits clearly outweigh risk and burdens or vice versa	Consistent evidence from randomized controlled trials (RCTs) without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect
Strong recommendation, moderate-quality evidence, Grade 1B	Benefits clearly outweigh risk and burdens or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on confidence in the estimate of effect and may change the estimate
Strong recommendation, low- or very-low-quality evidence, Grade 1C	Benefits clearly outweigh risk and burdens or vice versa	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate
Weak recommendation, high-quality evidence, Grade 2A	Benefits closely balanced with risks and burden	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient or society values. Further research is very unlikely to change confidence in the estimate of effect
Weak recommendation, moderate-quality evidence, Grade	Benefits closely balanced with risks and burden	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence	Best action may differ depending on circumstances or patient or society values. Higher-quality research may well have an important impact on confidence in the estimate of

Grade of Recommendation*	Benefit vs. Risk and Burden	Methodologic Quality of Supporting Evidence	Implications
Weak recommendation, low- or very-low-quality evidence, Grade 2C	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Outcome from observational studies, case series, or RCTs, with serious flaws or indirect evidence	Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate

\*The guideline developers use the wording recommend for strong (Grade 1) recommendations and suggest for weak (Grade 2) recommendations.

## Clinical Algorithm(s)

None provided

## Scope

## Disease/Condition(s)

Heparin-induced thrombocytopenia (HIT) with and without associated thrombosis

## Guideline Category

Management

Prevention

Screening

Treatment

## Clinical Specialty

Anesthesiology

Cardiology

Critical Care

Emergency Medicine

Family Practice

Hematology

Internal Medicine

Orthopedic Surgery

Pharmacology

Pulmonary Medicine

Surgery

Thoracic Surgery

## Intended Users

Advanced Practice Nurses

Health Care Providers

Hospitals

Nurses

Patients

Pharmacists

Physician Assistants

Physicians

## Guideline Objective(s)

- To update evidence-based recommendations for the use of anticoagulant therapy for the management of thromboembolic conditions
- To offer guidance for many common anticoagulation-related management problems
- To optimize patient-important health outcomes and the processes of care for patients who have experienced or are at risk for thrombotic events
- To describe the recognition, treatment, and prevention of heparin-induced thrombocytopenia (HIT)
- To update evidence-based recommendations for the use of antithrombotic and thrombolytic therapy for the management of thromboembolic conditions associated with HIT or suspected HIT

## Target Population

Patients receiving unfractionated or low-molecular-weight heparin considered at risk of heparin-induced thrombocytopenia (HIT) or in whom the exposure history of the patient is uncertain

## Interventions and Practices Considered

1. Platelet count monitoring combined with the 4Ts score for patients receiving heparin/low-molecular-weight heparin (LMWH)
2. Use of nonheparin anticoagulants (lepirudin, argatroban, danaparoid, bivalirudin, fondaparinux)
3. Use of platelet transfusions
4. Vitamin K antagonist (VKA), with monitoring of international normalized ratio (INR)
5. Special considerations for the following subgroups:
  - Patients with heparin-induced thrombocytopenia (HIT) complicated by thrombosis
  - Patients with renal insufficiency
  - Patient undergoing cardiac surgery
  - Patients undergoing percutaneous coronary interventions
  - Pregnant patients
  - Patients requiring renal replacement therapy
  - Patients with a past history of HIT

## Major Outcomes Considered

- New thrombosis
- Limb amputation
- Major bleeding
- Death due to thrombosis or bleeding
- Rate of false-positive and false-negative results in platelet monitoring

# Methodology

## Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

### General Methods

#### Defining the Clinical Questions—Population, Intervention, Comparator, and Outcome

The thrombosis expert on the Executive Committee along with the deputy editors took primary responsibility for defining the scope of the clinical questions that each article would address. For each question, the topic editor and deputy editor defined the relevant population, alternative management strategies (intervention and comparator), and the outcomes (i.e., population, intervention, comparator, and outcome [PICO] format). Each clinical question provided the framework for formulating study inclusion and exclusion criteria and guided the search for relevant evidence (systematic reviews and original studies). Panels typically restricted included studies to randomized controlled trials (RCTs) for intervention questions but included observational studies when there was a paucity of RCT data addressing an intervention and for questions of risk assessment. Readers can find these PICO questions in the first table of each article. One or more recommendations could be formulated for each clinical question.

#### Identifying the Evidence

To identify the relevant evidence, a team of methodologists and medical librarians at the Oregon Health & Science University Evidence-based Practice Center conducted literature searches of Medline, the Cochrane Library, and the Database of Abstracts of Reviews of Effects. For each article, the team conducted a search for systematic reviews and another for original studies encompassing the main populations and interventions for that article. These searches included studies indexed from week 1, January 2005, forward because Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th Edition (AT8) searches were carried out up to that date (search strategies are available on request). Many articles supplemented these searches with more-focused searches addressing specific clinical questions. When clinical questions had not been covered in AT8, searches commenced at a date relevant to each intervention.

Titles and abstracts retrieved from bibliographic database searches generally were screened in duplicate, and full-text articles were retrieved for further review. Consensus on whether individual studies fulfilled inclusion criteria was achieved for each study between two reviewers. If consensus could not be achieved, the topic editor and other topic panelists were brought into the discussion. Deputy editors reviewed lists of included studies from the database searches in order to identify any potentially missed studies. Additional studies identified were then retrieved for further evaluation.

Topic panels also searched the same bibliographic databases for systematic reviews addressing each PICO question. The quality of reviews was assessed using principles embodied in prior instruments addressing methodologic quality of systematic reviews, and wherever possible, current high-quality systematic reviews were used as the source of summary estimates. Reviews were also used to identify additional studies to complement the database searches.

### Specific Methods for This Guideline

For this guideline, the expert panel searched the PubMed English language literature from January 1976 to June 2010 using the following search terms: "heparin-induced thrombocytopenia," "clinical trial," "cohort," "randomized clinical trial," "argatroban," "lepirudin," "hirudin," "bivalirudin," "fondaparinux," "diagnosis," "laboratory assay," "clinical prediction rule," "platelet count monitoring," "coronary artery bypass," "cardiac surgery," "cardiopulmonary bypass" (CPB), "angioplasty," "transluminal percutaneous coronary," "treatment," "venous limb gangrene," "platelet transfusion," "renal replacement therapy," "hemodialysis," "hemofiltration," "pregnancy," "re-exposure," and "recurrence."

## Number of Source Documents

Not stated

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Approach to Rating Quality of Evidence

Study Design	Quality of Evidence	Lower if	Higher if
Randomized Trial →	High	Risk of bias -1 Serious -2 Very serious	Large effect +1 Large +2 Very large
	Moderate		
Observational Study →	Low	Inconsistency -1 Serious -2 Very serious	Dose response +1 Evidence of a gradient
	Very Low	Indirectness -1 Serious -2 Very serious  Imprecision -1 Serious -2 Very serious  Publication bias -1 Likely -2 Very likely	All plausible confounding +1 Would produce a demonstrated effect or  +1 Would suggest a spurious effect when result show no effect

## Methods Used to Analyze the Evidence

Decision Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

### General Methods

Assessing Studies and Summarizing Evidence

*Evaluating Risk of Bias in Individual Studies*

The expert panel developed and applied uniform criteria for evaluating the risk of bias associated with individual randomized controlled trials (RCTs) based on the criteria recommended by the Cochrane Collaboration (Table 1 in the methodology companion [see the "Availability of Companion Documents" field]). Although all authors assessed risk of bias for individual studies, because of resource limitations, the panel summarized the results of the risk of bias for only a minority of the recommendations. Readers can find these assessments in the online data supplements. For most recommendations for which such tables were not developed, Evidence Profiles that typically provide information on the risk



of bias in footnotes were developed.

The panel also developed specific criteria for assessing the risk of bias of observational studies (cohort studies with concurrent controls, cohort studies with historical controls, case-control studies, or case series). Again, these were based on the evidence-based domains recommended by the Cochrane Collaboration for observational studies.

Studies without internal comparisons were termed "cohort studies without internal controls" if they met the following criteria:

1. A protocol existed before the date of commencement of data collection.
2. A definition of inclusion and exclusion criteria was available.
3. The study reported the number of excluded patients.
4. The study conducted a standardized follow-up, including description of all of the following: schedule of follow-up, investigation of suspected outcomes, and criteria used to define outcomes.
5. The study reported all losses to follow-up.

The panel labeled studies that did not meet these criteria as "case series." No distinction was made between prospective and retrospective studies because although prospective studies may on average be of higher quality, individual prospective studies may have a significant risk of bias and specific retrospective studies may not. For questions related to risk assessment, the panel evaluated the risk of bias of individual studies using the following criteria: valid outcome assessment, including blinding when appropriate; adjustment for between-group differences; and minimal loss to follow-up.

### *Evaluating Quality of Bodies of Evidence*

The expert panel assessed evidence across studies on an outcome-by-outcome basis using criteria suggested by the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group. The expert panel defined quality of evidence as their confidence in the estimate of the effect to support a recommendation. RCTs start as high-quality evidence and observational studies as low-quality evidence. Additional factors that affect this rating of quality include the risk of bias; precision, consistency, and directness of results; likelihood of publication bias; and presence of very large effects. The American College of Chest Physicians (ACCP) adaptation of the GRADE system differs only in that the quality of a body of evidence can be high (A), moderate (B), or low (C); GRADE also provides a category for very-low-quality evidence. See the "Rating Scheme for the Strength of the Evidence" field.

Often, the panel found that the quality of the evidence differed across outcomes. For example, in assessing the quality of evidence for thienopyridines vs warfarin in patients undergoing percutaneous coronary interventions, the panel determined the evidence to be of moderate quality for mortality, nonfatal myocardial infarction, and revascularization but of low quality for major bleeding.

The panel then made a rating of the quality of the entire body of evidence bearing on the effect of alternative management strategies for each clinical question. In other words, the panel assessed the quality across outcomes, including both benefits and harms. Quality for each recommendation was the lowest quality rating of the outcomes judged as critical (as opposed to important, but not critical).

Most patient-important outcomes in this guideline are binary or yes-no outcomes (death, stroke, venous thromboembolism [VTE], myocardial infarction, bleeding). In general, relative effects are similar across subgroups of patients, including those with varying baseline risk. The evidence summaries (Evidence Profiles and Summary of Findings tables), therefore, include a presentation of relative effects (where possible as relative risks because they are easier to understand than odds ratios [ORs]) of intervention vs control management strategies.

Trading off desirable and undesirable consequences (e.g., thrombosis vs bleeding) requires, however, estimates of absolute effect. For example, in patients with atrial fibrillation, warfarin results in a 66% relative risk reduction in nonfatal stroke. This comes at a cost of inconvenience, lifestyle restrictions, and risk of bleeding. For patients with a CHADS (congestive heart failure, hypertension, age  $\geq 75$  years, diabetes mellitus, stroke) score of  $\geq 3$ , the 66% relative risk reduction translates into an absolute reduction of 6.3% (63 in 1,000) per year. Virtually all patients will consider this worthwhile. On the other hand, for patients with a CHADS score of 0, the 66% reduction translates into an absolute risk reduction of only 0.5% (5 in 1,000) per year. Many patients may consider this reduction not worth the undesirable consequences of warfarin use.

The panel calculated absolute effects by applying relative risks to estimates of control group risk. For instance, if control group risk of thrombosis is 4% and relative risk with an intervention is 50%, then the absolute difference between intervention and control is 4% of 50% or 2%, and the number needed to treat to prevent an episode of thrombosis is 100/2 or 50. In many cases, the Summary of Findings tables present effects as events prevented (or caused) per 1,000 patients. In this hypothetical example, the effect would be 20 events per 1,000 patients.

Whenever valid prognostic data were available from observational studies, they were used to estimate control group risks. When credible results from observational and prognostic studies were not available, risk estimates from control groups of RCTs were used.

### *Considering Subgroup-Specific Relative and Absolute Effects*

Whenever the expert panel identified credible evidence that the relative effects vary across distinguishable subgroups of patients (i.e., interaction between the intervention and a patient characteristic), the respective relative effects were considered separately. The panel then calculated the associated absolute effects.

Even when the relative effect is the same, the absolute magnitude of treatment effects may differ in patients with varying levels of risk. For instance, although the relative risk reduction of warfarin vs aspirin in stroke prevention for patients with atrial fibrillation is likely close to 50% across risk groups, this translates into an absolute risk reduction of <1% per year in the lowest-risk groups and ~5% per year in the highest-risk groups.

The expert panel included control group risks and absolute-effect estimates for different groups in the summaries of effect when (and only when) two conditions were present. First, they required validated prognostic models or, at the very least, credible strategies for clinicians to easily identify higher- and lower-risk patients. Second, the panel identified varying risk groups only when recommendations differed in strength or direction between groups. Both conditions were met, for instance, in the atrial fibrillation recommendations in which strong recommendations in favor of anticoagulation were restricted to the higher-risk patients.

### *Conducting Meta-analyses*

When pooled estimates of effects were not available from existing high-quality systematic reviews, the panel performed meta-analyses if the data were sufficiently homogeneous. When pooling two studies, they used a fixed-effects model. When three or more studies were available for generating a pooled estimate, they used a random-effects model as the primary analysis and a fixed-effects model as a secondary analysis. If there were discrepancies between the two, the panel considered the following reasons: If there was substantial heterogeneity leading to wider confidence intervals (CIs) with the random-effects model, the panel considered that model more trustworthy, and if the discrepancy was due to a single large dominant study with a result substantially different from smaller studies, they considered the fixed-effects model more trustworthy. The panel also assessed statistical heterogeneity using both a  $\chi^2$  test and  $I^2$  as well as assessed possible explanations of heterogeneity considering a priori-generated hypotheses.

### *Summary Tables*

When resources permitted, the expert panel used a standardized approach for summarizing the evidence and methodology of individual studies. These summaries appear in the online data supplements. Wherever possible, the expert panel reported nonfatal events (e.g., nonfatal stroke) so that there is no overlap with the number of fatal events reported.

For a large number of recommendations, the expert panel summarized the quality of the body of evidence (see the "Rating Scheme for the Strength of the Evidence" field) and estimates of relative and absolute effect of alternative management strategies using the methods of the GRADE Working Group. Evidence Profiles summarize the quality of the body of evidence and when evidence comes from randomized trials, generally include a presentation of reviewer assessment of risk of bias, precision, consistency, directness, and publication bias associated with each outcome. As specified in GRADE methodology, the overall quality of evidence represents the lowest quality of any critical outcome.

Evidence Profiles can be found in the online data supplement. The format for these tables was determined through a formal survey of panelists that evaluated the panelists' preferences for alternative presentations and the impact of these presentations on their understanding of the evidence. The text in the printed version of Antithrombotic Therapy and Prevention of Thrombosis, 9th ed (AT9) recommendations includes more succinct Summary of Findings tables, which include the overall quality assessment as well as the relative and absolute effect sizes for each outcome. Use of an associated computer program facilitated the production of the Evidence Profiles and Summary of Findings tables which are listed in the original guideline document.

### Specific Methods for This Guideline

The panel adhered to the general approach to developing recommendations described in the methodology above.

The primary efficacy outcome measures of interest were new thrombosis, limb amputation, major bleeding, and death (due to thrombosis or bleeding). In the cohort studies with historical controls, outcome events were counted if they occurred after treatment with the nonheparin anticoagulant was initiated, and from the date heparin was discontinued in the control group.

### *Value and Preferences*

Based on the relevant literature and the value and preference rating exercise conducted by the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines panel, the panel infer that from the patient's perspective, a venous thromboembolic event (e.g., pulmonary embolism [PE], proximal DVT) carries similar weight as a major bleeding

event (e.g., gastrointestinal bleeding event), and that a stroke carries 2.5 times the weight of a major bleeding event.

#### Platelet Count Monitoring Combined with the 4Ts Score for Patients Receiving Heparin/Low-Molecular-Weight Heparin (LMWH)

The panel conducted a decision analysis to determine the reduction in heparin-induced thrombocytopenia (HIT)-related thrombotic events that could be achieved in an ideal setting if the recommendations for platelet count monitoring, laboratory testing for HIT, and initiation of a direct thrombin inhibitor (DTI) were all followed. To reduce the potential for expensive testing and inappropriate treatment of patients with a low clinical probability of HIT, the panel assumed that platelet count monitoring would be done as part of a clinical assessment of the patients' probability of HIT using the 4Ts score (see Table 5 in the original guideline document for key model assumptions; Table 6 for data sources and model inputs). Table 7 in the original guideline outlines the summary of findings for this decision analysis.

## Methods Used to Formulate the Recommendations

Expert Consensus (Consensus Development Conference)

## Description of Methods Used to Formulate the Recommendations

### Composition and Selection of Topic Panel Members

The American College of Chest Physicians (ACCP) Antithrombotic Therapy and Prevention of Thrombosis, 9th ed (AT9) Executive Committee selected panel members for each article. A topic editor and a deputy editor led each of the AT9 panels issuing recommendations. The topic editor was the person primarily responsible for each article and was required to be a methodologist without serious financial or intellectual conflict of interest for any of the article's recommendations. In all but one case, the topic editor also was a clinician. The Executive Committee chose these individuals on the basis of their previous experience with guideline development and, in particular, their familiarity with methods developed by the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group. These topic editors and all panel members were approved by the ACCP Health and Science Policy (HSP) Committee after review of their conflict of interest disclosures.

Criteria for selection of the remainder of the panel members, including the deputy editor-thrombosis expert, were an established record in the relevant clinical or research area, international and gender representation, and an absence of financial conflicts of interest that were judged unacceptable. Some of the panelists had prior experience on ACCP guidelines in this area and represented the thrombosis community, but there was substantial turnover from the previous edition. After an international request for applications broadcast through multiple medical societies, the Executive Committee nominated individual topic editors and deputy editors and collaborated with them to identify and nominate other topic panel members.

The ACCP HSP Committee reviewed all nominees and approved all panel members after review of their curricula vitae and conflict of interest disclosures. Of 150 nominees, 137 were approved, 18 were approved with management of conflicts of interest (i.e., regular disclosures and review of ongoing conflicts as the process progressed), and 13 were disapproved as a result of the magnitude of financial conflicts of interest. Articles associated with recommendations included from seven to 14 panel members. Patients or representatives of specific stakeholder groups were not included on topic panels.

Each topic panel also included a frontline physician working in the relevant area who was neither an expert in thrombosis nor a methodologist or clinical investigator. These individuals were chosen in consultation with the topic editors and the ACCP HSP Committee. These clinicians were charged with the following: (1) proposing important real-world clinical questions on the prevention, diagnosis, and treatment of thrombosis that were not addressed in Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th Edition (AT8) and (2) reviewing the draft manuscripts and recommendations to assess the usability of the guidelines and the feasibility of implementation of AT9 recommendations.

To address issues of economic efficiency six health economist-physicians were included on the AT9 topic panels charged with making recommendations. These resource consultants were selected and approved through identical procedures to those for topic editors and panel members.

### Ensuring Consistency Across Articles

A number of strategies were used to ensure consistency across articles, and one panel member participated extensively in the formulation of clinical questions for each article. To ensure consistency of judgments regarding bleeding, another panel member was responsible for standardizing the approach to bleeding outcomes and participated in multiple topic panels. Additionally, to ensure consistency in the trade-offs between thrombotic

and bleeding events, all articles used the same ratings of values and preferences (described in more detail in the methodology companion [see the "Availability of Companion Documents" field]). Because some of the same evidence summaries were relevant to several articles, five individuals were chosen to participate in each of the articles addressing coronary artery disease, stroke, and peripheral arterial disease.

In AT9, prevention of venous thromboembolism (VTE) is addressed in three articles as opposed to a single article as was done in AT8. The prevention topic editors and deputy editors and those of the stroke article (which includes thromboprophylaxis recommendations) participated in multiple conference calls to develop and harmonize the approach to prevention and to ensure consistency among final recommendations. Topic editors consulted with one another when issues overlapped. For example, the decision regarding the use of a vitamin K antagonist, aspirin, and clopidogrel simultaneously in patients with atrial fibrillation, valvular disease, and intravascular stents is relevant for the atrial fibrillation, coronary, and peripheral arterial disease articles. Topic panels deferred to the Evidence-Based Management of Anticoagulant Therapy AT9 topic panel for recommendations related to the dosing and monitoring of anticoagulation therapies.

The AT9 Executive Committee met at least once a month and regularly issued statements of clarification of methods to topic editors and deputy editors (e.g., use of fixed- or random-effects models for meta-analysis), conflict of interest, preparation of tables, and issues of style and presentation. All these statements were communicated directly to the topic editors and deputy editors and made available in a central repository accessible to all AT9 panelists. The chair of the Executive Committee was available for resolving any challenging issues related to the aforementioned topics. Between September 2009 and September 2010, two members of the Executive Committee held regular (every 3 months), separate conference calls with each topic editor and deputy editor during which they addressed questions and concerns. Finally, the chair of the Executive Committee reviewed every article to ensure consistency of evidence presentation, evaluation, and writing style. Refer to the methodology companion for further information on the approach used to ensure consistent language in writing.

### Formulating Recommendations

Following approaches recommended by the GRADE Working Group, the topic editor, in some cases aided by a panelist without conflicts, formulated the draft recommendations. The formulation of recommendations considered the balance between the desirable and undesirable consequences of an intervention; the quality of evidence; the variability in patient values and preferences; and, on occasion, resource use issues. The recommendations were graded as strong when desirable effects were much greater than undesirable effects or vice versa. Strong recommendations were worded as "The expert panel recommends" and labeled 1. Recommendations were graded as weak when desirable effects were not clearly greater or less great than undesirable effects. Weak recommendations were worded as "The expert panel suggests" and labeled 2. The rating of the quality of the evidence—high, A; moderate, B; or low, C—is provided with the strength of each recommendation.

### Finalizing Recommendations

The topic panel members without primary conflicts discussed draft recommendations. Initial discussions generally led to a consensus at the article level on the quality of evidence and the direction and strength of recommendations. At least two members of the Executive Committee reviewed in detail drafts of articles, including recommendations. Written critiques were prepared and returned to the authors for revision. Articles were then made available to the entire AT9 panel.

Recommendations on which topic panels had difficulty coming to a consensus were discussed at a final conference in February 2011 attended by the topic editors and deputy editors and at least one other panel member from each article. Prior to the conference, all AT9 panelists updated their conflict of interest disclosures. The ACCP invited a number of clinical organizations with interest in the guideline topic to attend the final conference as observers.

At this final conference, a representative of each article presented potentially controversial issues in their article's recommendations. Following discussion, which included those present and those attending by video conference, all panelists without primary conflicts of interest voted on each recommendation. The voting process used a GRADE grid and required that for a strong recommendation,  $\geq 80\%$  of those voting had to agree that a strong recommendation was appropriate.

The AT9 Executive Committee members harmonized the articles and resolved remaining disagreements among them through facilitated discussion with topic editors and deputy editors without primary conflicts. All major correspondence and decisions at the final conference were recorded in written and audio formats and are available on request to [science@chestnet.org](mailto:science@chestnet.org).

See the methodology companion (see the "Availability of Companion Documents" field) for information on accounting for patient values and preferences in recommendations.

## Rating Scheme for the Strength of the Recommendations

Grade of Recommendation*	Benefit vs. Risk and Burdens	Methodologic Quality of Supporting Evidence	Implications
Strong recommendation, high-quality evidence, Grade 1A	Benefits clearly outweigh risk and burdens or vice versa	Consistent evidence from randomized controlled trials (RCTs) without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect
Strong recommendation, moderate-quality evidence, Grade 1B	Benefits clearly outweigh risk and burdens or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on confidence in the estimate of effect and may change the estimate
Strong recommendation, low- or very-low-quality evidence, Grade 1C	Benefits clearly outweigh risk and burdens or vice versa	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate
Weak recommendation, high-quality evidence, Grade 2A	Benefits closely balanced with risks and burden	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient or society values. Further research is very unlikely to change confidence in the estimate of effect
Weak recommendation, moderate-quality evidence, Grade 2B	Benefits closely balanced with risks and burden	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies	Best action may differ depending on circumstances or patient or society values. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate
Weak recommendation, low- or very-low-quality evidence, Grade 2C	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Evidence for at least one critical outcome from observational studies, case series, or RCTs, with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate

\*The guideline developers use the wording recommend for strong (Grade 1) recommendations and suggest for weak (Grade 2) recommendations.

## Cost Analysis

### General

#### Resource Use Issues

In addressing resource use (cost) issues in Antithrombotic Therapy and Prevention of Thrombosis, 9th ed (AT9), the expert panel followed previously developed principles. In particular, the panel restricted economic evaluation to recommendations in which it was plausible that resource use considerations might change the direction or strength of the recommendation and in which high-quality economic evaluations were available. When this was not the case, the panel did not consider resource use in the recommendations.

Six clinicians with the requisite expertise in decision and economic analyses participated in the guideline development process; each article had the benefit of one of these experts as a full committee member. The following subsections present key points in the process of considering resource

allocation issues in the recommendations.

### *Overview of the Process*

Panelists, in consultation with resource use consultants, determined questions for which resource use might change the direction or strength of recommendations. For those questions, the panel sought high-quality economic analyses. If such analyses were available, the panel applied the evidence regarding resource use to the relevant recommendation. If net costs or marginal cost-effectiveness ratios were very high, panelists considered rating down the quality of evidence for an intervention from high to low or possibly changing the direction of the recommendation using guides described in the section "Criteria for Resource Allocation Issues to Affect Recommendations—Thresholds for Cost-Effectiveness" in the methodology companion (see the "Availability of Companion Documents" field).

### *Identifying the Literature*

The Oregon Health & Science University Evidence-based Practice Center conducted thorough literature searches for economic analyses relevant to the different AT9 articles. The resource use experts supplemented these by searches focused on the specific questions of interest for each article. The searches were conducted in Medline and the Cochrane Central Register of Clinical Trials. On the basis that data from studies appreciably more than a decade old would not reflect the current situation, searches were restricted to published studies from 1999 forward. Thus, bibliographic database searches encompassed publications from January 1999 forward. The end date varied across articles and ranged between November 2009 and March 2010 when the searches were executed.

### *Evaluating the Evidence*

A standardized data extraction form was used to ensure uniform evaluation of the quality of relevant economic analyses. Quality assessment was based on published criteria and included specification of perspective of analysis (e.g., societal, health system), appropriateness of time horizon (preferably lifetime), use of high-quality evidence for probabilities and rates, use of high-quality sources for costs (e.g., primary data, Medicare payments, claims data as proxies), use of appropriate methods for measurement of preferences, and performance of sensitivity analyses to explore uncertainty (both deterministic and probabilistic).

### *Criteria for Resource Allocation Issues to Affect Recommendations—Thresholds for Cost-Effectiveness*

The results of economic analyses may either increase the strength of an otherwise weak recommendation or weaken the strength of a strong recommendation. If cost-effectiveness studies bolstered an already strong recommendation, no change to the recommendation was necessary. The panel chose the following thresholds for cost-effectiveness considerations affecting recommendations:

1. When the clinical evidence warrants a strong recommendation for A over B:
  - a. Strong recommendation favoring A when high-quality evidence from economic evaluations shows that A costs <3 times the gross domestic product (GDP) per capita (approximately US \$150,000) per quality-adjusted life year (QALY) gained relative to B
  - b. Weak recommendation favoring A when high-quality evidence from economic evaluations shows that A costs 3 to 5 times the GDP per capita (~\$150,000-\$250,000) per QALY gained relative to B
  - c. Weak recommendation favoring B when high-quality evidence from economic evaluations shows that A costs >5 times the GDP per capita (~\$250,000) per QALY gained relative to B
2. When the clinical evidence warrants a weak recommendation for A over B:
  - a. Strong recommendation favoring A if A results in cost savings of >10% to 20% of the GDP per capita (~\$5,000-\$10,000) relative to B (Cost savings must represent all downstream costs and not just the actual cost of the intervention, and analysis must demonstrate a high level of confidence that there is a cost savings.)
  - b. Continued weak recommendation favoring A when B is marginally more costly than A (<10% the GDP per capita)
  - c. Continued weak recommendation favoring A when A costs 0 to 5 times the GDP per capita per QALY gained relative to B
  - d. Weak recommendation favoring B if A costs >5 times the GDP per capita (~\$250,000) per QALY gained relative to B

### *Extension of Economic Analyses to Low- and Middle-Income Countries*

Although certain interventions may be cost-effective in high-income countries (e.g., <\$20,000 per QALY gained), in poor countries, \$20,000 gained per QALY may be prohibitive. The choice of a threshold will vary depending on who is making resource allocation decisions. To facilitate the use of already published cost-effectiveness analyses, the World Health Organization (WHO), through its WHO-CHOICE (Choosing Interventions that are Cost Effective) program has used criteria suggested by the Commission on Macroeconomics and Health. Interventions that cost <1 times the average per-capita income for a given country or region per QALY gained are considered very cost-effective. Interventions that cost up to three times the average per-capita income per QALY gained are still considered cost-effective, whereas those that exceed this level are not considered to be cost-effective. To facilitate this process, WHO has developed tables of such threshold values for different regions and

countries around the world. Thus, the thresholds discussed in the previous section have been defined in terms of GDP per capita. Although referencing thresholds for cost-effectiveness to average per-capita income in middle- and low-income countries can help to extend results of economic analyses performed in high-income countries, such analyses may be less relevant in low-income countries because of significantly different material and labor costs and, thus, may be difficult to extrapolate. Furthermore, the comparator strategies may not be feasible or customary in these locales.

#### Specific to This Guideline

A factor that influences the feasibility of platelet monitoring with 4Ts screening is the cost. Although individual platelet counts are inexpensive, the cost of the heparin-induced thrombocytopenia (HIT) assays and nonheparin anticoagulants can be substantial (e.g., in a formal cost-effectiveness analysis the cost of treating one patient with HIT with argatroban for 5 days was estimated at \$3,500-\$4,500 in the United States 2004 prices). The estimated cost in 2011, for the drug alone, for 5 days is \$5,000 US.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

The American College of Chest Physicians (ACCP) Health and Science Policy (HSP) Committee established a process for the thorough review of all ACCP evidence-based clinical practice guidelines. After final review by the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed (AT9) Executive Committee, the guidelines underwent review by the Cardiovascular and Pulmonary Vascular NetWorks of the ACCP, the HSP Committee, and the ACCP Board of Regents. The latter two groups had the right of approval or disapproval but usually worked with the topic panelists and editors to make necessary revisions prior to final approval. Both the HSP Committee and the Board of Regents identified primary reviewers who read the full set of articles, and the remaining HSP Committee members were responsible for reviewing several articles each. The reviewers considered both content and methodology as well as whether there was balanced reporting and adherence to HSP Committee processes. All reviewers were vetted through the same conflict of interest disclosure and management process described in the "Description of Methods Used to Formulate the Recommendations" field. Finally, the Editor in Chief of *CHEST* read and forwarded the manuscripts for independent, external peer review prior to acceptance for publication. No recommendations or assessments of the quality of the evidence could be changed without the express approval of the topic panel members, AT9 Executive Committee, HSP Committee, and ACCP Board of Regents.

This guideline is endorsed by the American Association for Clinical Chemistry, the American College of Clinical Pharmacy, the American Society of Health-System Pharmacists, the American Society of Hematology, and the International Society on Thrombosis and Haemostasis.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

Appropriate prevention, monitoring, and management of patients with heparin-induced thrombocytopenia (HIT)

### Potential Harms



- Platelet count monitoring is warranted when the benefits of early diagnosis and treatment of heparin-induced thrombocytopenia (HIT) exceed the potential harms of frequent platelet count monitoring, including cost, unnecessary anxiety and additional testing, unnecessary withdrawal of heparin, and the use of nonheparin anticoagulants with a higher bleeding risk. False negative results of platelet count monitoring may increase the risk of thrombosis if not treated with nonheparin anticoagulants; false positives may increase the risk of bleeding if treated with nonheparin anticoagulants.
- The rapid initiation of warfarin in patients with HIT may produce a pro-thrombotic state because the level of the natural anticoagulant, protein C, falls faster than prothrombin levels. This can lead to serious adverse events, such as warfarin-induced skin necrosis and venous limb gangrene (distal ischemic limb necrosis in the absence of arterial occlusion).
- There is no direct evidence supporting initiation of vitamin K antagonist (VKA) at a particular platelet threshold in patients with HIT. However, there is low-quality evidence suggesting a potential for substantial harm if a supratherapeutic international normalized ratio (INR) is reached while a patient with HIT still has a low platelet count and is receiving warfarin without concurrent treatment with a thrombin or factor Xa inhibitor.

## Qualifying Statements

### Qualifying Statements

- The evidence-based practice guidelines published by The American College of Chest Physicians ("ACCP") incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Guidelines are intended for general information only, are not medical advice, and do not replace professional medical care and physician advice, which always should be sought for any specific condition. Furthermore, guidelines may not be complete or accurate because new studies that have been published too late in the process of guideline development or after publication are not incorporated into any particular guideline before it is disseminated. The ACCP and its officers, regents, governors, executive committee, members and employees (the "ACCP Parties") disclaim all liability for the accuracy or completeness of a guideline, and disclaim all warranties, express or implied. Guideline users always are urged to seek out newer information that might impact the diagnostic and treatment recommendations contained within a guideline. The ACCP Parties further disclaim all liability for any damages whatsoever (including, without limitation, direct, indirect, incidental, punitive, or consequential damages) arising out of the use, inability to use, or the results of use of a guideline, any references used in a guideline, or the materials, information, or procedures contained in a guideline, based on any legal theory whatsoever and whether or not there was advice of the possibility of such damages.
- Through a comprehensive and systematic literature review, the ACCP's evidence-based clinical practice guidelines incorporate data from the existing peer-reviewed literature. This literature meets the prespecified inclusion criteria for the clinical research question, which ACCP considers, at the time of publication, to be the best evidence available for general clinical information purposes. This evidence is of varying quality from original studies of varying methodological rigor. The ACCP recommends that performance measures for quality improvement, performance-based reimbursement, and public reporting purposes should be based on rigorously developed guideline recommendations. However, not all recommendations graded highly according to the ACCP grading system (1A, 1B) are necessarily appropriate for development into such performance measures, and each one should be analyzed individually for importance, feasibility, usability, and scientific acceptability (National Quality Forum criteria). Performance measures developers should exercise caution in basing measures on recommendations that are graded 1C, 2A, 2B, and 2C, according to the ACCP Grading System as these should generally not be used in performance measures for quality improvement, performance-based reimbursement, and public reporting purposes.
- Limitations of Methods: Although encouraged to use Evidence Profiles and Summary of Findings tables for all recommendations, there were some for which the authors were unable to produce such tables. However, those recommendations used an evidence-based systematic review and assessment of relevant studies. Some recommendations would have benefited from meta-analyses that would have clarified aspects of the evidence. Although panelists were instructed in completing the value and preference rating exercise to estimate patient values and preferences rather than to use their own, it cannot be assured that they succeeded in all instances.

## Implementation of the Guideline

### Description of Implementation Strategy

An implementation strategy was not provided.



## Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Getting Better

Staying Healthy

### IOM Domain

Effectiveness

Safety

Timeliness

## Identifying Information and Availability

### Bibliographic Source(s)

Linkins LA, Dans AL, Moores LK, Bona R, Davidson BL, Schulman S, Crowther M. Treatment and prevention of heparin-induced thrombocytopenia: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012 Feb;141(2 Suppl):e495S-530S. [182 references] [PubMed](#)

### Adaptation

Not applicable: The guideline was not adapted from another source.

### Date Released

2004 Sep (revised 2012 Feb)

### Guideline Developer(s)

American College of Chest Physicians - Medical Specialty Society

### Source(s) of Funding

The Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines received support from the National Heart, Lung, and Blood Institute [R13 HL104758] and Bayer Schering Pharma AG. Support in the form of educational grants were also provided by Bristol-Myers Squibb; Pfizer, Inc; Canyon Pharmaceuticals; and sanofi-aventis US.

The sponsors played no role in the development of these guidelines. Sponsoring organizations cannot recommend panelists or topics, nor are they allowed prepublication access to the manuscripts and recommendations.

## Guideline Committee

American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel

## Composition of Group That Authored the Guideline

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## Financial Disclosures/Conflicts of Interest

All panelists were required to disclose both financial conflicts of interest, such as receipt of funds for consulting with industry, and intellectual conflicts of interest, such as publication of original data bearing directly on a recommendation. Financial and intellectual conflicts of interest were classified as primary (more serious) or secondary (less serious). The operational definition of primary intellectual conflicts of interest included authorship of original studies and peer-reviewed grant funding (government, not-for-profit organizations) directly bearing on a recommendation. The operational definition of primary financial conflicts of interest included consultancies, advisory board membership, and the like from industry. Topic editors had no primary conflicts of interest, as noted. Some deputy editors, who were clinical experts in the topic of the article, had relevant primary conflicts of interest. The American College of Chest Physicians (ACCP) Health and Science Policy (HSP) Committee deemed some of these conflicts serious enough to require "management." Management involved more frequent updates of disclosures than required of the approved panelists without any conflicts and recusal from activities relevant to that conflict.

Topic panel members, including the deputy editor, with primary conflicts related to a particular recommendation did not participate in the final deliberations that led to the decision regarding the direction or strength of a recommendation, nor did they vote on recommendations for which they

were primarily conflicted. Panelists with primary conflicts could, however, participate in discussions and offer their opinions on interpretations of the evidence. Readers will find a record of panelist conflicts of interest on a recommendation-by-recommendation basis in the online data supplement.

In summary, the authors have reported to *CHEST* the following conflicts of interest: Dr Linkins has two potential indirect financial conflict of interests based on a peer-reviewed grant received from the Heart and Stroke Foundation of Canada to conduct a research study evaluating a diagnostic assay (PaGIA) for HIT and a single lecture (paid an honorarium by Pfizer) that included a brief discussion about HIT. Dr Linkins also discloses primary intellectual conflict of interest for diagnosis of HIT (holds a peer-reviewed research grant from the Heart and Stroke Foundation) and secondary intellectual conflict of interest (published reviews on HIT). Dr Dans received funding from GlaxoSmithKline for research in an area unrelated to HIT. Dr Davidson received consulting fees from Bayer and Daiichi Sankyo, makers of synthetic oral anticoagulants currently in clinical trials, and expenses for travel to a Steering Committee meeting. Dr Crowther has served on various advisory boards, has assisted in the preparation of educational materials, has sat on data safety management boards, and his institution has received research funds from the following companies: Leo Pharma A/S, Pfizer Inc, Boehringer Ingelheim GmbH, Bayer Healthcare Pharmaceuticals, Octapharm AG, CSL Behring, and Artisan Pharma. Personal total compensation for these activities over the past 3 years totals less than US \$10,000. COL Moores and Drs Bona and Schulman have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Guideline panel members, including the chair, and members of the Health & Science Policy Committee are blinded to the funding sources. Further details on the Conflict of Interest Policy are available online at <http://chestnet.org> .

## Guideline Endorser(s)

American Association for Clinical Chemistry, Inc. - Professional Association

American College of Clinical Pharmacy - Medical Specialty Society

American Society of Health-System Pharmacists - Professional Association

American Society of Hematology - Medical Specialty Society

International Society on Thrombosis and Haemostasis - Professional Association

## Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Warkentin TE, Greinacher A, Koster A, Lincoff AM. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008 Jun;133(6 Suppl):340S-80S. [284 references]

## Guideline Availability

Electronic copies: Available to subscribers of *Chest - The Cardiopulmonary and Critical Care Journal* .

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

## Availability of Companion Documents

The following are available:

- Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141:7S-47S.
- Introduction to the ninth edition: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical guidelines. *Chest* 2012;141:48S-52S.

- Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;53S-70S.
- Patient values and preferences in decision making for antithrombotic therapy: a systematic review: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;e1S-e23S.
- Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;e44S-e88S.
- Antiplatelet drugs: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;e89S-e119S.
- New antithrombotic drugs: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;e120S-e151S.
- Approach to outcome measurement in the prevention of thrombosis in surgical and medical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;e185S-e194S.

Electronic copies: Available to subscribers of [Chest - The Cardiopulmonary and Critical Care Journal](#) .

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI on November 19, 2004. The information was verified by the guideline developer on January 12, 2005. This summary was updated by ECRI on March 6, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin sodium). This summary was updated by ECRI Institute on June 22, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This summary was updated by ECRI Institute on September 7, 2007 following the revised U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin). This summary was updated by ECRI Institute on March 14, 2008 following the updated FDA advisory on heparin sodium injection. This NGC summary was updated by ECRI Institute on November 24, 2008. The updated information was verified by the guideline developer on January 7, 2009. This summary was updated by ECRI Institute on July 27, 2010 following the FDA drug safety communication on Heparin. This NGC summary was updated by ECRI Institute on May 2, 2012.

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